REMARKS/ARGUMENTS

This amendment addresses the issues raised in the Office Action of June 16, 2010, a final rejection, and accompanies a Request for Continued Examination (RCE).

Claim 1 is above amended to include the restriction that the heating is to a temperature in the range 96°C to 140 °C (basis in page 17, line 8). This amendment means that claim 4 is now redundant and it has been deleted.

The Examiner has cited Ribier US 6,066,328 (US'328) against the novelty of claims 1, 3-5, 8, 10-14, 16-20 and 22. Landh et al, US 5,531,925 (US'925) has been cited against the novelty of claims 1-3, 6, 7 and 9-21 (note: claim 4 specifying a temperature range for the heating is not included in the second rejection). These documents (US'328 and US'925) were cited during international examination as D2 and D1 respectively.

As background information, the International Examiner raised similar objections in his Written Opinion and the Applicant filed a Demand for International examination on this case during the international phase. In Europe, the application granted with essentially the same claims as are currently pending in the US, solely on the basis of the arguments made in the Demand and the accompanying response.

In the response of March 18, 2010, Applicants pointed out that US '328 relates to the generation of a cream. The generation method disclosed therein provides *the formation* of vesicles by a method of heat treatment. No particles are present prior to this heat-fragmentation method, no active agent is incorporated by that method and no heating in a solution of active agent is disclosed. US '328 therefore discloses a method of fragmentation of a lipid composition but no method for incorporation of an active agent into such a composition. If there is no active agent present then it seems fanciful to believe that a method of incorporating an active agent is provided.

US '925 relates to a heating method applied in order *to disperse* a non-lamellar phase. There is no heating and cooling step carried out *on amphiphile particles* since

the particles do not exist prior to the heating step. Furthermore, there is no disclosure of heat treatment carried out in a solution of active agents. US '925 thus discloses a method of fragmentation, which might form particles suitable for use in the method of the present invention, but does not disclose that method, nor any particle formed or obtainable thereby.

In the second part of the current Office Action (pages 5-6) the Examiner responds to Applicant's previous arguments.

The Examiner considers that US '328 discloses "a method of amphiphillic particles" (presumably a method of formation of amphiphillic particles) comprising forming a dispersion of particles and heating the mixture with an aqueous drug followed by cooling. The Examiner refers to the examples, which he considers show phase A comprising amphiphillic compounds in dispersion with a particle size from 80-500 nm (col. 2, lines 35-60). The Examiner states that these particles are present before heat-treatment and are inherent to the formulation, with reference to the abstract. The Examiner considers that phase A is then combined with aqueous phase C comprising hydroxyproline (active agent) and heated to a temperature of 90 °C before being allowed to cool to room temperature (example 3). On this basis, the Examiner considers that US '328 teaches a dispersion of particles (phase A) mixed with a solution of active agent (phase C) and therefore anticipate the claims.

Claim 1 as above amended requires several features:

- the formation of a dispersion of particles
- where the particles contain at least one amphiphillic structuring agent
- then the dispersion must be heated to an elevated temperature
- the heating must take place in a solution of at least one active agent
- said heating must be in the temperature range 96 °C to 140 °C
- after heating, there must be cooling to around ambient temperature.

The first question, therefore, is whether there is disclosure in US '328 of a dispersion of particles *before* the other steps of the process.

Column 2, lines 35-60 clearly refers to the final emulsion *produced by the method of* US '328. Lines 52-60 state "The invention makes available particularly stable emulsions having fatty phase droplets of extremely small size which are coated with an extremely fine mono- or oligolamellar layer... The mean size of the coated oily globules is less than 500 nanometres and preferably less than 200 nm for the formulations of milk and cream type, and it is less than 80 nm for transparent or opalescent formulations.", i.e. it is the *final emulsion* which contains particles of 80-500 nm, rather than any initial dispersion of particles.

This is supported by the abstract, "The present invention relates to a cosmetic or dermatological composition comprising an emulsion of oil-in-water type formed of oily globules... which are dispersed in an aqueous phase.". It is clearly the final product of US '328 which is disclosed as comprising "oily globules".

The Examiner considers that these two sections of the application disclose or teach that phase A of the examples comprises amphiphillic compounds in dispersion. However, both of these sections relate to the final product and there is no cross-reference to the examples or phase A.

Column 6, lines 62 to column 7, line 23 describes the process used in the examples of US '328. The "oily phase" A1 and the "aqueous phase" B are heated separately to 80 °C and then mixed and stirred at this temperature before being homogenized to provide an oil-in-water emulsion, which is cooled to room temperature. The oily phase A2 is then added and the mixture is stirred and homogenized. Column 7, lines 20-23 clearly state that phase C, when present, is added to the A1+B+A2 emulsion and the mixture stirred and homogenized at room temperature. There is no heating, no heating in a solution of active agent, and no cooling involved in this process. Furthermore, there is no heating in the particular temperature range stipulated by amended claim 1.

The Examiner has specifically referred to example 3 of US '328 and considers this to disclose phase A being combined with aqueous phase C comprising hydroxyproline (active agent) and heated to a temperature of 90 °C before being allowed to cool to room temperature. In fact, as described above, all the examples follow the same process, whereby an emulsion is formed from phases A1+B+A2 and phase C (where present) is mixed into this *at room temperature*.

The Examiner appears to have misunderstood example 3, the mid-section of which discloses the combination of the components of phase C1. The three lipids constituting the vesicle wall are heated to 115 °C, forming a transparent liquid mixture, which is then cooled to 90 °C. The remaining components of phase C1 are then added to this lipid mixture at the same temperature, 90 °C (i.e. the temperature is maintained, not increased and there is no further heating). The mixture is then cooled and homogenized at 60 °C, and cooled to room temperature forming phase C1. When cool, phase C1 is mixed with phase C2 to form phase C. Phase C is then mixed at room temperature with the emulsion formed from phases A1+B+A2.

Hence, at the very least, there is no disclosure in US '328 of the mixture of phase A with phase C followed by heating, nor of heating to the specific temperature range required by amended claim 1. There is also no explicit disclosure of the heating of a dispersion of particles in a solution of active agent, or that the particles must contain an amphiphillic structuring agent.

For the above reasons, Applicants continue in their belief that the claims were novel over US '328 and are rendered even more clearly so by the introduced temperature range.

The Action contains only two anticipation rejections; there are no rejections under § 103. However, for completeness, the following observations are provided. US '328 is concerned with the absorption of cosmetic or dermatological skin care compositions and

bears no relation to the problem of active-agent loading which is addressed by the pending application. Furthermore, since the introduced temperature range is not used in US'328, there is no danger that the high-loading effect demonstrated in the present case might be inherently present in the prior art. The pending claims are inventive.

The Examiner considers US '925 teaches a method of forming amphiphillic particles comprising forming a dispersion of amphiphillic particles (abstract, column 16, lines 15-26), followed by equilibrating said material in a solution of active agents (column 10, lines 9-25, and column 10, line 66 to column 11, line 11). This equilibration is at an elevated temperature of 37 °C, followed by homogenization at room temperature. The Examiner appears to consider a cooling step is therefore implicitly disclosed here.

The abstract discloses particles comprising an interior phase of a particular type and a surface phase of a different type. The abstract also discloses "a method of preparing such particles by creating a local dispersible phase... by fragmenting the homogeneous phase...".

There is no disclosure in the abstract (or anywhere else in this document) of the combination of formation of a dispersion followed by heat treatment in the temperature range 96 °C to 140 °C in a solution of active agent. Claim 4 was not included in this rejection, so by implication, the amendment to claim 1 renders at least method claims 1-3 and 5-9 novel.

Column 16, lines 15-26 simply lists various polymers which are examples of suitable fragmentation agents. Again, there is no disclosure or teaching here of the features of the process of the invention.

Most significantly, the Examiner has referred to columns 10-11. It appears that the Examiner has misunderstood the disclosure of this section of US '925. In particular, the section from line 66 of column 10 to line 11 of column 11 discloses a particular method of fragmentation with the objective of *forming* particles. This is achieved by the

co-equilibration of the starting material with an amphiphilic substance at elevated temperature. The *starting material* is not a dispersion of particles comprising an amphiphilic structuring agent, as required by applicants' claim 1, nor is there disclosure here of heating *in a solution of active agent*.

It is clear, therefore, that US '925 relates to a heating method applied in order *to disperse* a non-lamellar phase. There is no heating and cooling step carried out on amphiphile particles since the particles do not exist prior to the heating step. Furthermore, there is no disclosure of heat treatment carried out in a solution of active agents nor to the required temperatures. US '925 thus discloses a method of fragmentation, which might form particles suitable for use in the method of the present invention, but does not disclose that method, nor any particle formed or obtainable thereby.

With regard to claim 10, the Examiner maintains that the particles themselves are anticipated by the disclosures of the prior art. The Examiner's argument here is essentially that the same drug-loading is inherent in the compositions of the citations. However, since the process of formation is different, as explained above, the current invention allows a higher drug loading than has previously been disclosed, hence the loaded particles are both new and inventive. It is clearly demonstrated in the examples of the present application than equilibration with the same components *does not* provide incorporation of an active agent at a level as high as is achievable by the present method. Indeed, this is one of the key and most unexpected features of the present invention. Thus, without carrying out the methods of the present claims including heating of particles in a solution of active agent at the specified temperature range, the particles of the present invention are not achievable. Therefore the particles themselves embody the new and non-obvious nature of the invention.

All outstanding issues have been addressed and this application is in condition for allowance. Should any minor issues remain outstanding, the Examiner should contact the undersigned at the telephone number listed below so they can be resolved expeditiously without need of a further written action.

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Arthur R. Crawford
Reg. No. 25,327

ARC:sjg
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100